Impact of prenatal diagnosis on the prevalence of live births with Down syndrome in the eastern half of Switzerland 1980-1996

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Abstract: OBJECTIVES AND METHODS To investigate the impact of prenatal diagnosis on trisomy 21 live births, we collected all prenatal and postnatal trisomy 21 cases (n = 1096) in the eastern half of Switzerland for the years 1980-1996. RESULTS Despite increasing prenatal detection rates of trisomy 21 foetuses (an increase of 169% in the last 5 versus the first 5 years of the study period) and subsequent termination of pregnancies, the number of liveborn Down syndrome children remained constant. The reason is a shift towards a higher mean maternal age from 28 to 30 years between 1980 and 1996. If mean maternal age at delivery was considered, the observed increase of trisomy 21 conceptions matched well with the calculated figures. CONCLUSION If the tendency to have pregnancies at a more advanced age continues and if the use of prenatal diagnosis does not increase, an increase in incidence of Down syndrome liveborns may be expected in the first decades of the 21st century.

Originally published at:
Binkert, Franz; Mutter, Michael; Schinzel, Albert (2002). Impact of prenatal diagnosis on the prevalence of live births with Down syndrome in the eastern half of Switzerland 1980-1996. Swiss Medical Weekly, 132(33-34):478-484.

Peer reviewed article

Impact of prenatal diagnosis on the prevalence of live births with Down syndrome in the eastern half of Switzerland 1980–1996

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Summary

Objectives and Methods: To investigate the impact of prenatal diagnosis on trisomy 21 live births, we collected all prenatal and postnatal trisomy 21 cases (n = 1096) in the eastern half of Switzerland for the years 1980–1996.

Results: Despite increasing prenatal detection rates of trisomy 21 foetuses (an increase of 169% in the last 5 versus the first 5 years of the study period) and subsequent termination of pregnancies, the number of liveborn Down syndrome children remained constant. The reason is a shift towards a higher mean maternal age from 28 to 30 years between 1980 and 1996. If mean maternal age at delivery was considered, the observed increase of trisomy 21 conceptions matched well with the calculated figures.

Conclusion: If the tendency to have pregnancies at a more advanced age continues and if the use of prenatal diagnosis does not increase, an increase in incidence of Down syndrome liveborns may be expected in the first decades of the 21st century.

Key words: trisomy 21; Down syndrome; epidemiology; incidence; prenatal diagnosis; trends in incidence

Introduction

Trisomy 21 is the most frequent single chromosome aberration at birth [1]. Free trisomy, i.e. occurrence of 3 chromosomes 21, comprises about 95% of all trisomies 21 [2, 3] and is due to (mostly meiotic) nondisjunction occurring predominantly in the female gamete [4, 5]. The positive correlation between advanced age of the mother at conception and the risk for a Down syndrome child is well known, although the aetiology is still unclear [6–12]. Because of this age dependency, the overall incidence of newborns with trisomy 21 is mainly influenced by the maternal age distribution in a population [13]. However, incidence at birth is strongly dependent on the proportion of pregnant women deciding for prenatal diagnosis because of advanced childbearing age (≥35 years) or abnormal results of either foetal ultrasound [14–16] or biochemical screening [17, 18] and subsequent termination of pregnancies with chromosome aberrations.

The issue whether the increasing use of prenatal diagnosis is dramatically reducing the number of liveborn children with Down syndrome, was controversially discussed in Switzerland [19]. Here, in about 10% of all pregnancies, prenatal cytogenetic examination is performed [20]. Therefore we collected all prenatally and postnatally diagnosed cases with trisomy 21 in the years 1980–1996 in the eastern half of this country. Switzerland lacks a central registry for birth defects. However, it is assumed that more or less all individuals, in whom Down syndrome is suspected, undergo a chromosome examination. Since the data obtained corresponded well with the frequencies expected in our population, we could estimate the influence of prenatal diagnosis on the incidence of liveborn children with trisomy 21. Our results are compared with recent trends in other western countries.

Patients and methods

Financial support: Zürich canton

We included all karyotyped trisomy 21 cases (n = 1096), either live- or stillborn or prenatally diagnosed in the years 1980–1996, whose mothers were living in the eastern half of Switzerland at the time of birth (cantons of Appenzell, Aargau, Glarus, Graubünden, Lucerne, Sankt Gallen, Schaffhausen, Schwyz, Tessin, Thurgau, Unter-

walden, Uri, Zug, Zurich). In order to obtain complete data, all other cytogenetic laboratories in Switzerland were asked to contribute trisomy 21 cases from this area. The following data were collected for the liveborn: date of birth and blood sampling, age of the mother, living place of the mother at birth of the child and karyotype. For the prenatal cases, date of sampling and material (chorionic villi, amniocytes, fetal blood), fetal karyotype, month and year of delivery or of termination of the pregnancy as well as domicile and age of the mother were collected. The expected birth date of a foetus was calculated on the basis of the biparietal diameter or the crown-rump length at the day at which the foetal sample was collected, or the first day of the last menstrual period of the mother. Data on the outcome of the pregnancies were obtained through questionnaires.

Yearly age distribution of the female population in every canton of the study area, number of births and age distribution of the mothers at birth were obtained from the Federal Office of Statistics at Berne, Switzerland.

Postnatally diagnosed cases of trisomy 21 and prenatally diagnosed cases continuing pregnancy to birth summarize to "liveborn observed" and, by dividing this number by the total number of births, to "incidence observed".

The impact of prenatal diagnosis on the rate of trisomy 21 newborn was estimated by adding all terminated pregnancies with trisomy 21 foetuses to the liveborn children with Down syndrome. Pregnancies with unknown outcome were considered as terminated to prevent an underestimation of the prenatal contribution to the total number of trisomy 21 cases.

To evaluate the number of trisomy 21-children that would have been born in case no prenatal diagnosis had been performed at all, the trisomy 21 foetuses estimated to be spontaneously lost during pregnancy had to be deduced from the number of liveborn. For this calculation we used the models of Hook (about 50% probability for a spontaneous abortion or stillbirth until birth if diagnosed before the 18th week, and about 35% thereafter [21]) and Halliday (31% and 18%, respectively [22]). The resulting numbers were added to the numbers of liveborns with trisomy 21, giving the "corrected number of liveborn". Dividing the latter by the total number of births during this period resulted in the "corrected incidence".

Using maternal age specific estimates [8] expected numbers of newborns with trisomy 21 were calculated. The comparison between the expected and observed numbers of liveborns with Down syndrome revealed whether or not the ascertainment was complete.

Changes in the incidence of liveborns with observed trisomy 21 as well as the use of prenatal diagnosis and their influence on the frequency of trisomy 21 births were determined by calculating mean square successive differences and applying a run-test [23]. Changes in the trend were verified by the test suggested by Cochran [23].

Results

Prenatal diagnoses

A total of 396 cases of trisomy 21 were detected prenatally between 1980 and 1996, including 266 through from amniocyte and 130 from chorionic villus chromosome examination. One hundred and twenty-one invasive procedures were performed before the 16th week of pregnancy, and 275 thereafter. Twenty-two of these pregnancies (5.6%) were carried to term: 6 by decision of the parents when the diagnosis was made between the 11th and 16th week of pregnancy, and 16 diagnosed after the 27th week when no termination is performed anymore. Three hundred and thirty-three foetuses (84.6%) were aborted. Nine pregnancies (2.3%) ended as intrauterine foetal death or stillbirth. The outcome of the pregnancy could not be determined in 30 cases (7.6%). The proportion in which a pregnancy with a prenatally detected trisomy 21 foetus was terminated fluctuated between 90 and 95%.

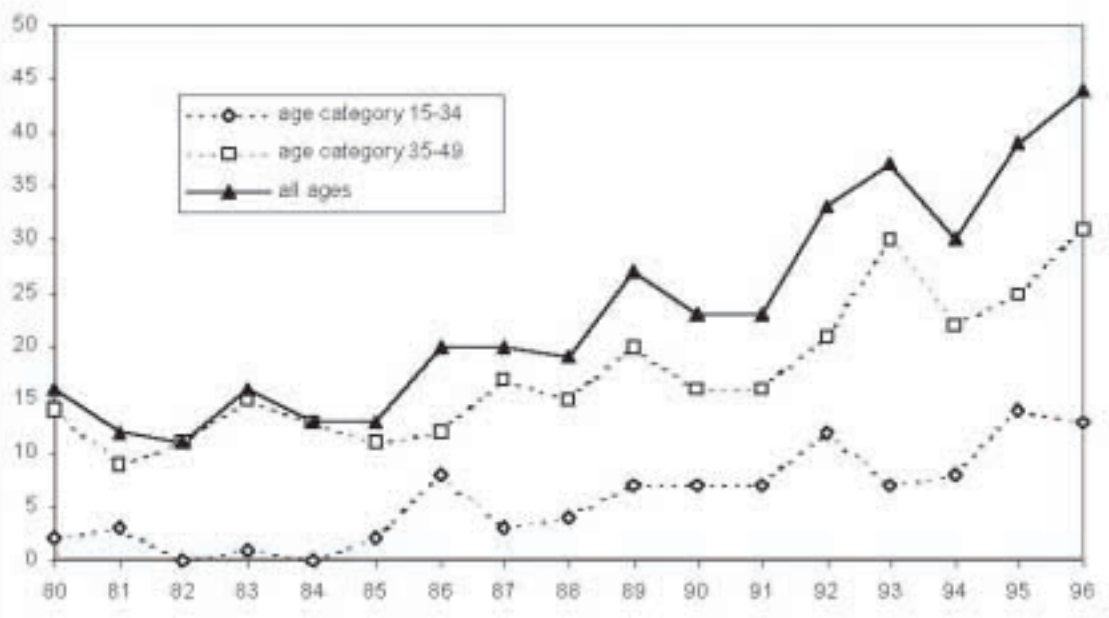


Figure 1

Number of prenatal diagnoses of trisomy 21 for the years 1980–1996 in the age categories "all ages", "15–34 years" and 35–49 years" of the pregnant women. Abscissa: calendar year. Ordinate: number of prenatal diagnoses with trisomy 21.

The number of trisomy 21 cases diagnosed prenatally remained stable during the years 1980–1985, but clearly increased thereafter (figure 1). We analyzed 68 cases during the first five years of the study, and 183 during the last five years, an increase of 169%. At birth, 91% of the mothers were 35 years or older during the first five years. The absolute number of prenatally diagnosed trisomy 21 foetuses from these "old" mothers increased steadily since 1986 and doubled between 1992 and 1996. Mothers of trisomy 21 foetuses younger than 35 years were rare during the years 1980–1984 (9% of the total); however their proportion increased to 29.5% in 1996.

Postnatal results

A total of 722 liveborns with trisomy 21 were karyotyped after birth. The absolute numbers fluctuated irregularly with a low of 22 cases in the year 1984 and highs in the years 1989 and 1990 with 57 cases each (fig. 2). Pooling the values over periods of 5 years, 144 cases were counted between 1980 and 1984, 245 (an increase of 70%) between 1987 and 1991, and 231 in the last 5 years of the study (60% more than in 1980–1984).

The proportion of the 20–24-year-old mothers among all mothers of a trisomy 21 child diminished from 13% in 1980–1984 to 7% between 1992 and 1996. This proportion also decreased from 27% to 23% in the age group 25–29. However, it remained similar at 31–33% for the 30–34-year-old women, and increased from 24 to 30% in the age group "35 and older". The incidence of cytogenetically confirmed liveborn children with trisomy 21 fluctuated between 0.54 per 1000 live births (1/1851) in 1984 and 1.32 (1/757) in 1989. The overall incidence for the years 1980–1996 was 1.00 per 1000 live births.

Proportion of the prenatally diagnosed trisomies 21

We also noticed changes in the proportion of the prenatally diagnosed trisomies 21 among all karyotyped trisomie 21 cases in our series (table 1). Until 1991, about ⅓ were discovered prenatally. From 1991 to 1996 the proportion increased to nearly ½. It stayed constantly high in the age group "35 and older": for the 35–39-year-old women the value varied between 43 and 63%, for the age group 40–44 it varied between 75 and 80%, and for the 44 and older mothers between 80 and 100%. By contrast, in the younger mothers the percentage increased in the age group 20–24 from 0% in the 1980–1984 period to 11% during 1992–1996, for the age group 25–29 it increased from 5to 26% throughout the same time, and from 8 to 32% in the 30–34-year old group.

Type of aberration and sex

Three hundred and seventy-four (94.4%) of the prenatally analysed trisomies 21 and 670 (95.7%) of the postnatally detected cases were free trisomies; 14 (3.5%) and 12 (1.7%) respectively were mosaics, and 8 (2.0%) and 18 (2.6%) respectivelywere translocation-trisomies.

Two hundred and twelve (53.5%) of the prenatal cases and 365 (52.1%) of the postnatal cases were males, 183 (46.2%) and 335 (47.9%) respec-

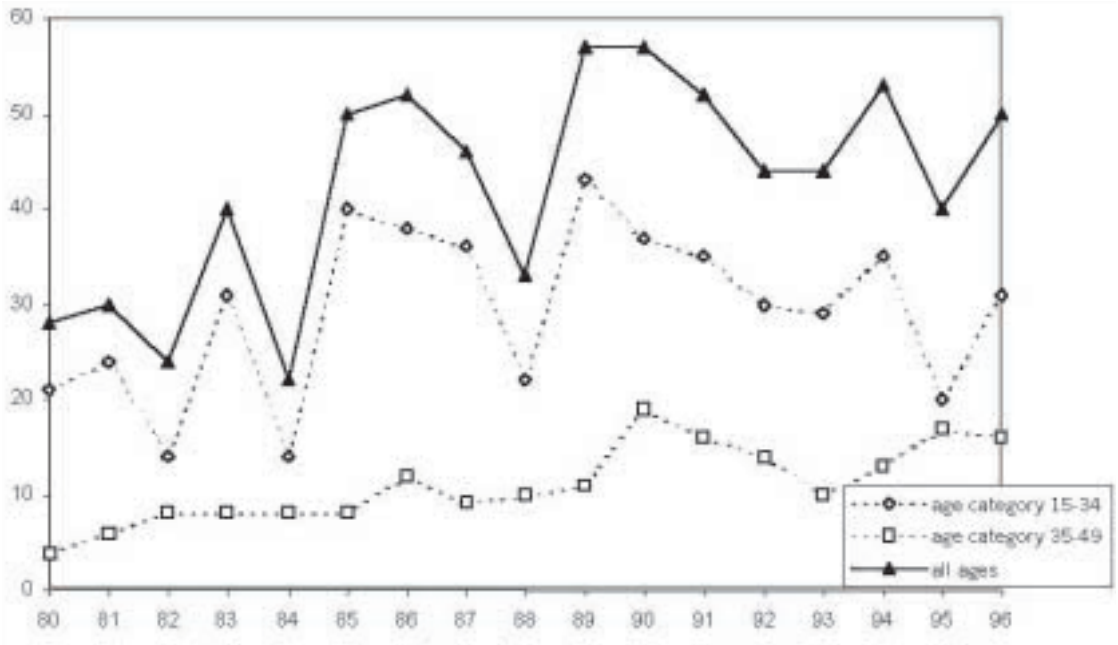
Table 1

Prenatally diagnosed trisomies 21 in proportion of all cytogenetically diagnosed trisomies 21.

maternal age categories (years)	calendar years		
	80–84	87–91	92–96
15–19	0.0%	0.0%	0.0%
20–24	0.0%	8.0%	11.1%
25–29	4.9%	15.8%	25.7%
30–34	8.2%	14.9%	32.4%
35–39	51.9%	43.0%	62.8%
40–44	79.5%	76.8%	75.4%
44–49	100.0%	100.0%	83.3%
all ages	32.2%	32.0%	45.5%

Figure 2

Number of births observed with trisomy 21 for the years 1980–1996 in the maternal age categories "all ages", "15–34 years" and "35–49 years".



tively were females. The sex of one prenatal case was not recorded.

Expected trisomies 21

The basis for the calculations were detailed information on the reproductive female population (women aged 15 to 49) in our study area and their births provided by the Federal Office of Statistics of Switzerland. The number of women at reproductive ages raised continuously from 831 237 in 1980 to 933 237 in 1996. At the beginning of the nineties, changes in subgroups could be observed: the group of women aged 20–29 began to decrease and was outnumbered by the age group 30–39 by 1996. In the year 1980, all women of the whole reproductive female population gave birth to 39 879 children. This number raised to 45 447 in 1992, but fell again to 43 558 in 1996. The proportion of the mothers between 20 and 24 decreased throughout the whole study period, the number of mothers between 25 and 29 increased until the beginning of the nineties, decreasing thereafter. The proportion of the mothers aged 30 and over increased steadily outnumbering mothers of the younger age groups in 1996, thus leading to a shift from mothers in their twenties to mothers in their thirties.

Proportion of diagnosed trisomies 21 in the population and influence of prenatal diagnosis

After correction for prenatal losses, prenatally diagnosed and subsequently aborted cases were added to the liveborn, thus determining the incidence of newborn with trisomy 21 if no prenatal diagnosis would have been performed at all in the study population. A good match was found for the expected and effectively karyotyped numbers after 1984 (fig. 3). Using the model of Hook, the birth rate of trisomy 21 children was diminished by prenatal diagnosis by 20% in the period 1987–1991 and by 31% in 1992–1996. The reduction for mothers aged 40 and over was always high during those 2 periods: 64 and 60%, respectively, in the 40–44-year-old mothers, as well as 100% and 70% respectively in the "45 and older" group. In the younger age groups the impact of prenatal diagnosis on the reduction of trisomy 21 live births was increasing with time. It increased for the age group 35–39 from 29% in the period 1987–1991 to 46% in 1992–1996, from 9% to 21% for the 30–34-years-old females and from 6% to 15% for the 25–29 group. For the 20–24-year-old females the values were 6% and 3%, respectively.

Due to the lower risk estimates of prenatal loss in the model of Halliday the influence of prenatal diagnosis is 3.5% to 5% higher than in the model of Hook (fig. 3).

Discussion

Prenatally diagnosed trisomies 21

As expected, the number of prenatally diagnosed trisomy 21 cases increased from 1986 to 1996 (fig. 1) with significant values ($p < 0.05$ in a run-test) for the total numbers and the maternal age groups of 25–29, 30–34 and 35–39 years of age. It stayed constant from 1980–1985, because at that time prenatal cytogenetic diagnosis was almost exclusively performed in "older mothers". Introduction of chorionic villus sampling [24], ultrasonographic screening (e.g. nuchal translucency [16]) in the second half of the eighties as well as maternal

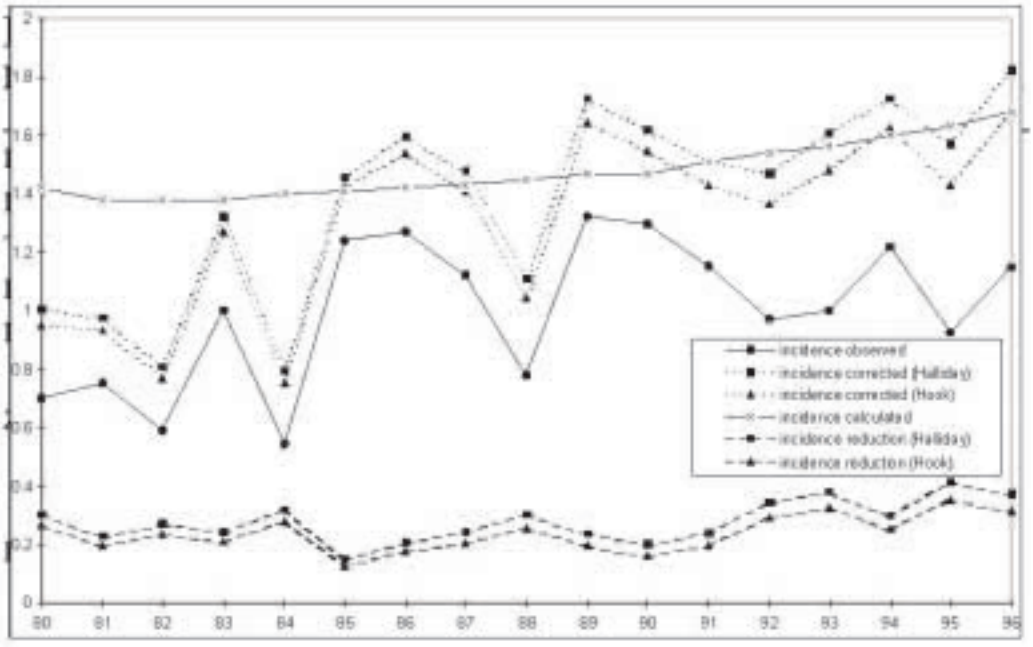


Figure 3

Incidence of births with Down syndrome in the years 1980–1996 and the influence of prenatal diagnosis. Abscissa: calendar year. Ordinate: number of children with Down syndrome in 1000 births.

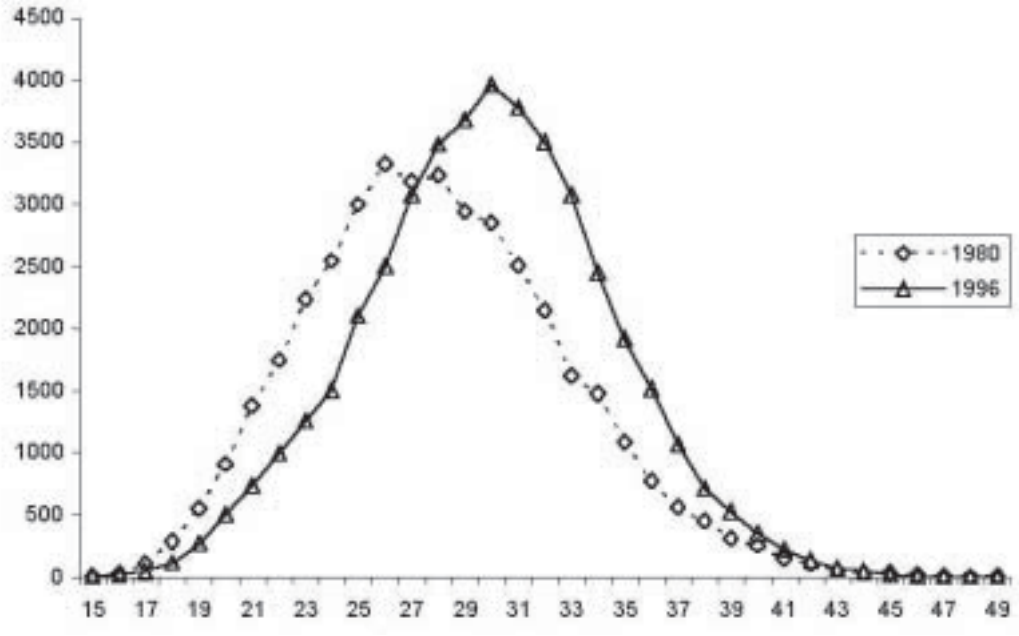


Figure 4

Age of the mothers at birth in the years 1980 and 1996. Abscissa: mother's age in years. Ordinate: number of mothers.

serum screening in the first half of the nineties [18] successively led to the identification of a 2.5-fold higher number of trisomy 21 foetuses in the middle of the nineties versus in the period 1980–1985. All these additional measurements led to an increased detection rate mainly in mothers aged less than 35 years.

Parents' decisions after prenatal diagnosis of trisomy 21

Only 9 out of 375 women diagnosed before the 25th week of pregnancy decided to carry their pregnancy to term. Six foetuses were born. Three pregnancies ended by intrauterine foetal death. The other couples decided to terminate the pregnancy. The decision is unknown in 30 cases, but most of them were probably interrupted. The increasing prenatal detection rate of trisomy 21 therefore should have led to a decrease of liveborn trisomies 21 after 1985, unless other factors would have counteracted this process.

Liveborn trisomies 21 and proportion of prenatally diagnosed trisomies 21

The number of liveborn trisomy 21 children surprisingly increased between 1980 and 1985 and leveled off thereafter (fig. 2). Whereas the proportion of the mothers aged 35 and older still increased slightly from 24 to 30% over the study period, the proportion of the less than 30 year old mothers decreased (fig. 4). Nevertheless the proportion of prenatally diagnosed trisomies 21, being about one third of all diagnosed trisomies 21 in the eighties, expectably increased thereafter to 40% and more (fig. 3) due to an increase in the number of detected foetuses from younger mothers.

Type of aberration and sex

With about 95% of free trisomies and 2.5% each for mosaics and translocations, the distribution of the cytogenetic subgroups of Down syndrome is in agreement with figures from the literature as is the sex ratio (53% males and 47% females) [3, 25].

Expected trisomies 21

Looking at the mothers' age at birth in the study area and the number of births between 1980 and 1996, a clear shift from mothers in their twenties to mothers in their thirties (fig. 4) can be recognized, elevating the peak maternal age at birth from 26 years in 1980 to 30 years in 1996 (mean maternal age 28.0 years and 29.84 years respectively). Using the specific age risk ratios by Cuckle et al. [8], the expected number of Down syndrome births would have increased through this shift from about 1.42/1000 in 1980 to 1.68/1000 in 1996, if no prenatal diagnosis with subsequent abortion would have been performed at all.

Proportion of diagnosed trisomies 21

Using the models of Hook et al. [21] and Halliday et al. [22], the evaluation of our data shows a complete ascertainment for the years 1985 and later. A detailed analysis of the earlier results indicated a deficit of cases in some cantons. This is most likely due to incomplete cytogenetic ascertainment of clinically diagnosed cases of Down syndrome. Not considering the possibility of familial translocation-trisomies, many physicians considered cytogenetic confirmation to be unnecessary if the phenotype was classical of Down syndrome.

Applying the model of Hook, the birth rate of Down syndrome children was reduced by prenatal diagnosis by about 20% (mainly due to the age indication) in the early eighties. The reduction increased to about 31% in the period 1992–1996, because of the introduction of more thorough ultrasound examinations, of the improvement of the skill of the examiners, and of maternal serum screening, all of which mainly affected women less

than 35 years of age. Because of lower estimates of prenatal losses, these values are slightly higher (3.5 to 5%) using the model of Halliday. However, due to the shift to higher maternal ages at conception over the years with a consequently higher probability of trisomic foetuses, all these measurements could only counterbalance an increase of the number of Down syndrome newborns.

Comparison with the literature

Several authors stated that the incidence of liveborns with Down syndrome stayed constant or even slightly increased since the mid-eighties even in countries with increasing numbers of prenatal diagnoses. The cause is an increase of the mean maternal age at birth and the rising proportion of mothers aged more than 35 years in many western countries since the mid-seventies [26–40]. This latter proportion was about 15% in Switzerland in 1996 [20]. As in other industrialized countries, women born during the period of the baby boom after the second world war (1945–1963) started to dominate in Switzerland among pregnant women in the nineties. As a consequence of reduced birth rates due to oral contraception, they overruled in numbers the women under 30 [34, 38, 41]. These facts and the tendency to postpone family planning should dramatically increase the incidence of liveborn children with Down syndrome (30–35, 37, 38, 41]. In our study area, the increase was from 1.42/1000 in 1980 to 1.68/1000 in 1996. According to different calculations [38, 41] this increase will continue in the first decade of the new Millennium. Cornel et al. [38] predicted an incidence of 2.2/1000 for the year 2001 in the Netherlands without prenatal diagnosis and selective abortion. Similar trends are expected in Switzerland due to comparable demographic and lifestyle conditions. Only two studies showed a reduction of Down syndrome birth rates due to increased use of maternal serum screening: a Scottish investigation [42] showing a decrease of the incidence from 1.08/1000 in 1990–1991 to 0.77/1000 in 1992–1994, and a Wallonian study [43] revealing a decrease from 0.95/1000 in 1984–1983 to 0.66/1000 in 1993–1998.

Although 65 to 75% of the trisomy 21 conceptions of mothers aged 35 and over were prenatally diagnosed between 1992 and 1996 in our study area, the total incidence of liveborn trisomy 21 children decreased only by 30–36%, because 85% of all children and 70% of all children with trisomy 21 are still born to mothers aged less than 35 years at delivery. Because the mean maternal age at birth is increasing, only better risk stratification and discovery of yet unknown risk factors in younger women could counterbalance an increase [33, 38, 44]. A change could be reached by more frequent use of the maternal serum screening [20].

As the life expectancy of newborns with Down syndrome increased since the fifties [45–47] a higher prevalence of individuals with Down syndrome is expected in the first decade of the 21st century in Switzerland as well as in most other countries in Western Europe.

We would like to thank the cytogenetic laboratories which contributed cases to our study (Genetica AG in Zurich, University Childrens Hospital in Basel; Institute Dr. Viollier AG in Basel; Division of Medical Genetics, University Hospital in Lausanne; Enzym Labor Dr. H. Weber AG in St. Gallen and Institute of Pathology, University of Bern) and all the parents and medical doctors who helped us to get a nearly complete follow up. We also thank Dr. M. Roos from the Institute of Social and Preventive Medicine of the University of Zurich for statistical support.

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References

1 Schinzel A. Down-Syndrome. In Leiber, Die klinischen Syndrome, Band 1: Krankheitsbilder, Burg G, Kunze J, Pongratz D, Scheurlen PG, Schinzel A, Spranger J, eds. Urban und Schwarzenberg: München 1996:211–2.
2 Antonarakis SE. 10 years of Genomics, chromosome 21 and Down syndrome. Genomics 1998;51:1–16.
3 Stoll C, Alembik Y, Dott B, Roth MP. Study of Down syndrome in 238 942 consecutive births. Ann Genet 1998;41:44–51.
4 Antonarakis SE, Avramopoulos D, Blouin JL, Talbot Jr CC, Schinzel AA. Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. Nature Genet 1993;3:146–50.
5 Antonarakis SE, Petersen MB, McInnis MG, Adelsberger PA, Schinzel AA, Binkert F, et al. The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms. Am J Hum Genet 1992;50:544–50.
6 Hook EB, Lindsjö A. Down syndrome in livebirths by single-year maternal age interval in a Swedish study: comparison with results from a New York State study. Am J Hum Genet 1978; 30:19–27.
7 Ferguson-Smith M, Yates JRW. Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative european study on 52 965 amniocenteses. Prenat Diagn 1984;4:5–44.
8 Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. Br J Obstet Gynaecol 1987;94:387–402.
9 Halliday JL, Watson LF, Lumley J, Danks DM, Sheffield LJ. New estimates of Down syndrome risks at chorionic villus sampling, amniocentesis and livebirth in women of advanced maternal age from a uniquely defined population. Prenat Diagn 1995;15:455–65.
10 Hecht CA, Hook EB. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: a proposed revised rate schedule for use in genetic and prenatal screening. Am J Med Genet 1996;62:376–85.

11 Bray I, Wright DE, Davies C, Hook EB. Joint estimation of Down syndrome risk and ascertainment rates: a meta-analysis of nine published data sets. Prenat Diagn 1998;18:9–20.
12 Huether CA, Ivanovich J, Goodwin BS, Krivchenia EL, Hertzberg VS, Edmonds LD et al. Maternal age specific risk rate estimates for Down syndrome among live births in whites and other races from Ohio and Metropolitan Atlanta, 1970–1989. J Med Genet 1998;35:482–90.
13 Källen B, Knudsen LB. Effect of maternal age distribution and prenatal diagnosis on the population rates of Down syndrome – a comparative study of nineteen populations. Hereditas 1989; 110:55–60.
14 Benacerraf BR, Barss VA, Laboda LA. A sonographic sign for the detection in the second trimester of the fetus with Down's syndrome. Am J Obstet Gynecol 1985;151:1078–9.
15 Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. Br Med J 1992;304:867–9.
16 Savoldelli G, Binkert F, Achermann J, Schmid W. Ultrasound screening for chromosomal anomalies in the first trimester of pregnancy. Prenat Diagn 1993;13:513–8.
17 Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P. Maternal serum screening for Down's syndrome in early pregnancy. Br Med J 1988;297:883–7.
18 Zimmermann R, Schmid W, Binkert F, Achermann J, Huch R, Huch A. Trisomie-21-Screening mit AFPplus in der östlichen Landeshälfte der Schweiz. Schweiz Med Wochenschr 1995;125: 1286–93.
19 Bonfranchi I. Menschen mit Trisomie 21 sterben aus. Soziale Medizin 1996;1:38–9.
20 DeLozier-Blanchet CD, Wisser J. Prenatal diagnosis in Switzerland. Eur J Hum Genet 1997;5(suppl 1):77–83.
21 Hook EB, Mutton EM, Roy I, Alberman E, Bobrow M. The natural history of Down syndrome conceptuses diagnosed prenatally that are not electively terminated. Am J Hum Genet 1995;57:875–81.
22 Halliday JL, Watson LF, Lumley J, Danks DM, Sheffield LJ. New estimates of Down syndrome risks at chorionic villus sampling, amniocentesis and livebirth in women of advanced maternal age from a uniquely defined population. Prenat Diagn 1995;15:455–65.
23 Sachs L. Angewandte Statistik. Anwendung statistischer Methoden. 8. Auflage. Springer: Berlin, Heidelberg, New York, 1997:481–8.
24 Hugentobler W, Binkert F, Haenel AF, Schaetti D. Die Chorionzotten-(Plazenta-) Biopsie im II. und III. Trimenon: Neue Perspektiven der Pränataldiagnostik. Geburtsh u Frauenheilkd 1987;47:729–32.
25 Gardner RJM, Sutherland GR. Down syndrome. In: Chromosome abnormalities and genetic counseling. New York: Oxford University Press, 1989:137–43.
26 Nazer J, Hubner ME, Cifuentes L, Ramirez R, Catalan J, Ruiz G. Aumento de la incidencia del sindrome de Down y su posible relacion con el incremento de la edad materna. Rev Med Chil 1991;119:465–71.
27 De Vigan C, Vodovar V, Vérité V, Dehé S, Goujard J. Current French practices for prenatal diagnosis of trisomy 21: population-based study in Paris, 1992–97. Prenat Diagn 1999;19: 1113–8.
28 De Vigan C, Vodovar V, Dufouil C, Goujard J. Trisomy 21 and maternal age: developing trends in Paris 1981–1990 [French]. Rev Epidém et Santé Publ 1992;40:369–78.
29 Hahn JA, Shaw GM. Trends in Down's syndrome prevalence in California, 1983–1888. Paediatr Perinat Epidemiol 1993;7: 450–60.
30 Krivchenia E, Huether CA, Edmonds LD, May DS, Guckenberger S. Comparative epidemiology of Down syndrome in two United States populations, 1970–1989. Am J Epidemiol 1993; 137:815–28.
31 Stoll C, Alembik Y, Dott B, Roth MP. Recent trends in the prevalence of Down syndrome in north-eastern France. Ann Génét 1994;37:179–83.
32 Aymé S. Apport des registres à la décision en santé publique: l'exemple de la trisomie 21. Rev Epidém et Santé Publ 1996; 44(Suppl 1):82–9.
33 Huether CA, Haroldson K, Ellis PM, Ramsay CN. Impact of prenatal diagnosis on revised livebirth prevalence estimates of Down syndrome in the Lothian region of Scotland, 1978–1992. Genet Epidemiol 1996;13:367–75.
34 Olsen CL, Cross PK, Gensburg LJ, Hughes JP. The effects of prenatal diagnosis, population ageing and changing fertility rates on the live birth prevalence of Down syndrome in New York State, 1983–1992. Prenat Diagn 1996;16:991–1002.
35 Baird PA, Sadovnick AD. Maternal age specific rates for Down syndrome: changes over time. Am J Med Genet 1988;29: 917–27.
36 Modell B, Kuliev AM. Impact of public health on human genetics. Clin Genet 1989;36:286–98.
37 Staples AJ, Sutherland GR, Haan EA, Clisby S. Epidemiology of Down syndrome in South Australia, 1960–1989. Am J Hum Genet 1991;49:1014–24.
38 Cornel MC, Breed ASPM, Beekhuis JR, Meerman GJ te, Kate LP ten. Down syndrome: effects of demographic factors and prenatal diagnosis on the future livebirth prevalence. Hum Genet 1993;92:163–8.
39 Hoshi N, Hattori R, Hanatani K, Okuyama K, Yamada H, Kishida T, et al. Recent trends in the prevalance of Down syndrome in Japan, 1980–1997. Am J Med Genet 1999;84:300–45.
40 Rosch C, Steibicker V, Kropf S. Down's syndrome: the effect of prenatal diagnosis and demographic factors in a region of the eastern part of Germany. Eur J Epidemiol 2000;16:627–32.
41 Goodwin BA, Huether CA. Revised estimates and projections of Down syndrome births in the United States and the effects of prenatal diagnosis utilization, 1970–2002. Prenat Diagn 1987;7:261–271.
42 Carothers AD, Boyd E, Lowther G, Ellis PM, Couzin DA, Faed MJW, et al. Trends in prenatal diagnosis of Down syndrome and other autosomal trisomies in Scotland 1990 to 1994, with associated cytogenetic and epidemiological findings. Genet Epidemiol 1999;16:179–90.
43 Verloes A, Gillerot Y, van Maldergem L, Schoos R, Herens C, Jamar M, et al. Major decrease in the incidence of trisomy 21 at birth in south Belgium: mass impact of triple test? Eur J Hum Genet 2001;9:1–4.
44 Bell J, Hilden J, Bowling F, Pearn J, Brownle A, Martin N. The impact of prenatal diagnosis on the occurence of chromosome abnormalities. Prenat Diagn 1986;6:1–11.
45 Fryers T. Survival in Down's syndrome. J Ment Defic Res 1986; 30:101–10.
46 Baird PA, Sadovnick AD. Life expectancy in Down syndrome. J Paediatr 1987;110:849–54.
47 Hayes C, Johnson U, Thornton L, Fogarty J, Lyons R, O'Connor M, et al. Ten-year survival of Down syndrome. Int J Epidemiol 1997;26:822–829.

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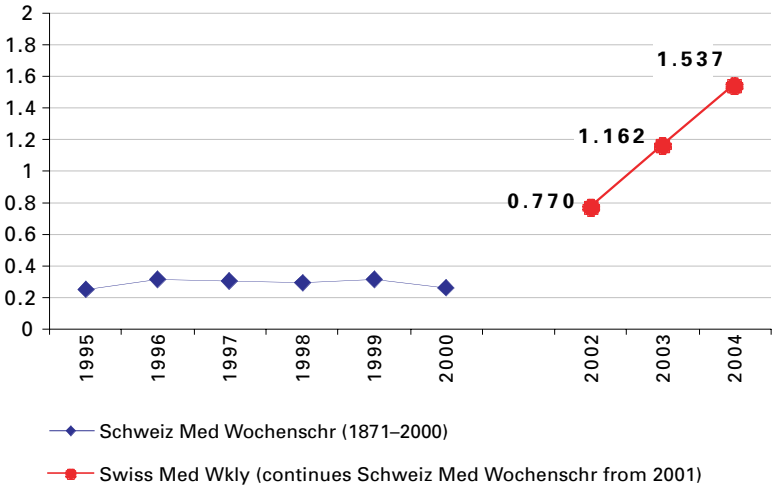

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